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DOI: https://doi.org/10.1016/j.biopsych.2013.09.013

To be submitted to Biological Psychiatry

Behavioral Responses to Catecholamine Depletion in Unmedicated, Remitted Subjects with Bulimia Nervosa and Healthy Subjects

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Key Words:

Bulimia Nervosa, Norepinephrine, Dopamine, Catecholamine Depletion, Pathophysiology, Behavioral Effects.

Word count abstract: 241
Word count article: 3982
Figure: 1
Table: 1

Abstract

Background: Bulimia Nervosa (BN) has been associated with dysregulation of the central catecholaminergic system. An instructive way to investigate the relationship between catecholaminergic function and psychiatric disorder has involved behavioral responses to experimental catecholamine depletion (CD). The purpose of this study was to examine a possible catecholaminergic dysfunction in the pathogenesis of bulimia nervosa.

Methods: CD was achieved by oral administration of alpha-methyl-para-tyrosine (AMPT) in 18 remitted female subjects with BN (rBN) and 31 healthy female controls. The study design consisted of a randomized, double blind, placebo-controlled crossover, single-site experimental trial. The main outcome measures were bulimic symptoms assessed by the Eating Disorder Examination-Questionnaire. Measures were assessed before and 26, 30, 54, 78, 102 hours after the first AMPT/ placebo administration.

Results: In the experimental environment (controlled environment with a low level of food cues) rBN subjects had a greater increase in eating disorder symptoms during CD compared with healthy controls (condition × diagnosis interaction, $p<0.05$). In the experimental environment rBN subjects experienced fewer bulimic symptoms than in the natural environment (uncontrolled environment concerning food cues) 36 hours after the first AMPT intake (environment × diagnosis interaction, $p<0.05$). Serum prolactin levels increased significantly, and to a comparable degree across groups, following AMPT administration.

Conclusions: This study suggests that rBN is associated with vulnerability for developing eating disorder symptoms in response to reduced catecholamine neurotransmission after CD. These findings support the notion of catecholaminergic dysfunction as a possible trait abnormality in BN.

Introduction

Bulimia nervosa (BN) is a psychiatric disorder characterized by recurrent episodes of binge eating and inappropriate compensatory behavior to prevent weight gain. The pathophysiology of BN is poorly understood, however, there is growing evidence that neurobiological vulnerabilities contribute to the pathogenesis of BN. Bulimia nervosa has been associated with dysregulation of central catecholaminergic system especially with decreased norepinephrine (NE) neurotransmission (1, 2). Dopamine (DA) has been implicated in the valuation of the rewarding properties of food (3) and in addiction (4), which are likely related to the pathogenesis of BN.

One instructive technique of assessing the relationship between catecholaminergic function and psychiatric disorders has involved the behavioral responses to catecholamine depletion (CD) achieved by oral administration of alpha-methyl-paratyrosine (AMPT) (5-7). AMPT is a competitive inhibitor of the rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase (8), and temporarily decreases catecholamine transmission by depleting central dopamine and norepinephrine stores, evidenced by reduced concentrations of catecholamines and their metabolites in plasma, urine and cerebrospinal fluid (9, 10) and decreased occupancy of striatal DA receptors by DA (11).

Most studies using CD were conducted in affective disorders (7, 12-14). In BN, several studies using tryptophan depletion (TD) have demonstrated a relationship between diminished serotonin activity and lowered mood, irritability, body image concerns and loss of control of eating (15-18). No study has used CD so far to evaluate the roles played by norepinephrine and dopamine in the pathophysiology of BN.

Monoamine depletion may not induce psychiatric symptoms in untreated acutely ill patients (15, 19), possibly due to a ceiling effect. The marked depressive responses following CD in subjects in the remitted phase of major depressive disorder who either were medicated with norepinephrine reuptake inhibiting antidepressant drugs (12-14) or were drug free (5, 7)

raised the possibility that manifesting specific symptoms following catecholamine depletion may constitute a neurobiological trait-marker for depression (6).

The purpose of this study was to identify a potential trait-like hypersensitivity to catecholamine depletion in BN by measuring the CD-induced behavioral responses in remitted subjects with BN (rBN). We hypothesized that CD would induce more eating disorder symptoms in rBN subjects than in healthy controls. Given that the risk of BN is associated with the risk of mood and anxiety disorders (20), we also predicted that CD would induce mood and anxiety symptoms in remitted subjects with BN.

Methods and Materials

Female subjects aged 19 to 39 years who had previously met DSM-IV criteria for BN and had been in remission from BN for at least 6 months (index subjects; n= 18; length of illness, mean (months) = 53.7 ; time in remission, mean (months) = 29.2) or had no history of any psychiatric disorder and no major psychiatric condition in first degree relatives (control subjects; n= 31) took part in this study. The screening visit included a diagnostic interview with a psychiatrist, the Structured Clinical Interview for DSM-IV, (21) and a physical examination. Both study groups were recruited by advertisements in local newspapers and announcements at the University of Zurich and the Swiss Federal Institute of Technology Zurich (ETH). Exclusion criteria for participation were current Axis I psychiatric disorders, a lifetime diagnosis of psychosis, major medical or neurological illness, psychoactive medication exposure within the last 6 months, lifetime history of substance dependence, pregnancy, suicidal ideation, and a history of suicide attempts. Remitted subjects with a history of BN (rBN) had been in remission for at least 6 months, more precisely they had no recurrent episodes of binge eating and no recurrent inappropriate compensatory behavior in order to prevent weight gain during the last 6 months (mean time in remission from BN= 29.2 months (SD=23.6), range: 6–84 months) at the time of study participation.

All subjects gave written, informed consent before participation. The study protocol was approved by the ethics committee of the Canton Zurich. The sample of this study overlaps with the sample of prior published data (22, 23). We used a randomized, double-blind, placebo-controlled, crossover design in which each subject underwent 2 identical sessions separated by at least 7 days in which they received either AMPT or placebo. Each session included 2 days at the Department of Psychiatry and Psychotherapy of the University Hospital of Zurich. On a segregated floor, a one-bed room with separate lavatory was available for all participants. Thus, participants had no contact with other hospitalized subjects. None of the rBN subjects had been hospitalized at the Department of Psychiatry and Psychotherapy before. During hospitalization, participants received regular non-vegetarian meals with standardized amounts of calories (day 1 at 7pm 650 kcal; day 2 at 7:30am 650 kcal and at 12pm 700 kcal).

For subsequent 3 days after each trial, subjects were contacted daily by telephone for follow-up interviews. In order to avoid any risk of adverse reaction a body weight-adjusted AMPT dose of 40 mg/kg body weight orally, to a maximum of 4g, over 22 hours (on day 1 at 9am, 12pm, and 7pm; on day 2 at 7am) was administered. During sham depletion, subjects received inactive placebo on day 1 at 9am and 12pm and 25mg diphenhydramine orally on day 1 at 7pm and on day 2 at 7am because AMPT frequently induces mild sedation. To prevent the formation of crystalluria during AMPT administration, subjects were instructed to drink at least 2 L of water daily. Possible adverse reactions were assessed regularly (26, 30, 54, 78, 102 hours after the first AMPT/ placebo administration) during hospitalization by a medical examination including blood pressure measurement and for subsequent 3 days after each trial within the daily telephone follow-up interview.

In each session blood samples were drawn 26 hours after the first AMPT dose in order to measure serum prolactin levels.

Behavioral ratings were conducted immediately before the first AMPT/ placebo intake (pre-challenge) and 26, 30, 54, 78, 102 hours after the first AMPT/ placebo administration.

Bulimic symptoms were assessed using the German Version of the Eating Disorder Examination-Questionnaire (EDE-Q) (24). EDE-Q is a 28-items self-report scale originated from the Eating Disorder Examination interview (EDE) (25, 26) designed to measure behavioral and cognitive features of eating disorders. Respondents indicate the value of particular feelings and attitudes towards eating behavior and body concerns over a definite time frame. Six of the 28 items assess the frequencies of eating disorder-related behavior in terms of number of binge eating episodes and compensatory behavior. These items do not contribute to scale score. An EDE-Q global score and 4 separate EDE-Q subscales scores for the subscales: 1 “control of eating / drive for thinness”; 2 “urge to eat / fear of binge eating”; 3 “weight concerns”; 4 “feeling fat / body dissatisfaction” can be derived from the instrument. For the purpose of this study the EDE-Q was adapted to a shorter time frame from past 28 days used in the original version (24) to past 12 hours in order to measure bulimic symptoms in response to AMPT or placebo. We tested this adapted scale in a pilot study. Based on our clinical assessments we came to the conclusion that it provides valid data. Additional behavioral ratings included the Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Beck Anxiety Inventory (BAI), Snaith-Hamilton Pleasure Scale (SHAPS) and Stanford Sleepiness Scale (SSS).

Full factorial linear mixed models with restricted maximum likelihood estimation were applied to determine the effects of condition (cond), diagnosis (dx), and time on each behavioral measure. SPSS subcommand for fixed effects: /FIXED=cond dx time cond*dx cond*time dx*time cond*dx *time | SSTYPE(3). Mixed models effects were computed based on change scores for each behavioral measure. For each condition (AMPT/ Placebo) and each participant change scores were calculated by subtracting the baseline (time point 0h)

from the score of each time point (26h, 30h, 54h, 78h and 102h). For all models a random effect for the subjects was included.

Because of the crossover study design, period was handled as 2*2(and 5 respectively) repeated measures. SPSS subcommand: /REPEATED= sequence*time|SUBJECT(id) COVTYPE(covst), where sequence captures the real sequence of AMPT/Placebo administration (randomly assigned to each patient). For each behavioral measure an appropriate covariance structure (covst) for the residuals was chosen considering the lowest Akaike's Information Criterion (AIC). A first order ante-dependence covariance structure (AD1) was best for the EDE-Q, a first-order factor analytic structure (FA1) for MADRS, a heterogenous first-order autoregressive structure (ARH1) for YMRS and BAI, a first-order autoregressive structure (AR1) for SHAPS and an AD1 for SSS.

Estimated marginal means regarding the interaction between diagnosis and condition allowed analyzing the diagnostic groups separately.

The analyses of the behavioral ratings EDE-Q, MADRS, BAI, SHAPS and SSS refer to the time in the controlled environment (time points 26h, 30h) since the main hypothesis applied to this condition and time frame. An exception represented the YMRS where a different time frame was considered (time points 26h, 30h, 54h, 78h, 102h), given that hypomanic symptoms were observed not before 48h after the first AMPT administration in our previous study (27).

To determine whether the environment had an effect on bulimic symptoms the experiment time frame of 102 hours was divided into two parts: controlled environment vs. uncontrolled environment. The controlled environment refers to the time of the stay at the Department of Psychiatry and Psychotherapy (time points 26h, 30h). By contrast, the uncontrolled environment refers to the time after the stay at the Department of Psychiatry and Psychotherapy (time points 54h, 78h, 102h).

In order to assess details regarding the type of BN symptoms we ran exploratory analyses on the EDE-Q subscales.

To verify whether past episodes of depression (n=4), history of anorexia nervosa (n=6) and the intake of psychotropic drugs (n=6) had an impact on the obtained results within the rBN group, the effect of these variables was also analyzed using linear mixed models.

To evaluate the relationship between CD-induced bulimic symptoms (EDE-Q) and other clinical scales (MADRS, YMRS, BAI, SHAPS, and SSS) in the controlled environment mixed models including clinical scales as covariates were applied.

The inclusion of a period effect and its interactions did not lead to important changes of the results of this study nor showed period any significant effect; as result, we did not include a period effect in the analyses reported in this article. The results of analyses on raw scores instead of change scores did not change the main findings of this study, either. As a result, we will only report the analyses on change scores, assuming they are more conclusive than the raw score analyses.

Analyses were performed using SPSS 18.0 statistical software (SPSS Inc, Chicago, Illinois). The statistical significance level was set at alpha= 0.05.

Results

Demographic and clinical characteristics of the subject sample are summarized in **Table 1**. **Figure 1** shows the behavioral responses in rBN and control subjects after AMPT/ placebo administration. In the controlled environment (time points 26h, 30h) there was a significant condition × diagnosis interaction for bulimic symptoms assessed by the EDE-Q (EDE-Q global score, $F_{1,41.9}$=4.19, p=0.047). rBN subjects reported more bulimic symptoms in the conditions where they received AMPT compared to the placebo condition ($F_{1,41.4}$=4.78, p=0.03), whereas AMPT did not induce bulimic symptoms in controls ($F_{1,42.6}$=.27, p=0.61).

Moreover, there was a significant condition × time interaction for bulimic symptoms assessed by the EDE-Q (EDE-Q global score, $F_{1,81.7}$=6.81, p=0.01).

The triple interaction of diagnosis × condition × time (EDE-Q global score, $F_{1,81.7}$=4.71, p=0.03) was significant too. The effects of diagnosis (EDE-Q global score, $F_{1,51.7}$=2.52, p=0.12), condition (EDE-Q global score, $F_{1,41.9}$=2.01, p=0.16) and time (EDE-Q global score, $F_{1,83.9}$=1.44, p=0.23) did not reach significance. There was no significant diagnosis × time interaction (EDE-Q global score, $F_{1,83.4}$=2.77, p=0.10). The type of environment (controlled vs. uncontrolled) had a significant influence on the experience of bulimic symptoms (environment × diagnosis interaction, $F_{1,70.3}$=4.77, p=0.03). In the controlled environment rBN subjects experienced significantly fewer bulimic symptoms than in the uncontrolled environment ($F_{1,71.4}$=17.84, p<=0.001), whereas this effect was much smaller in control subjects ($F_{1,68.0}$=4.24, p=0.04).

In the controlled environment, none of the subjects experienced any binge and/or purge episodes in response to AMPT vs. placebo, whereas in the uncontrolled environment (54h after the first AMPT intake) 1 rBN subject in the AMPT condition showed a binge-eating episode without subsequent compensatory behavior.

Exploratory analyses regarding EDE-Q subscales showed a triple interaction of diagnosis × condition × time for the subscale 2 “urge to eat / fear of binge eating” ($F_{1,91.3}$=6.15, p=0.01) and subscale 4 “feeling fat / body dissatisfaction” ($F_{1,70.3}$=6.69, p=0.01). Moreover, there was a significant condition × time interaction on subscale 3 “weight concerns” ($F_{1,77.5}$ =4.56, p=0.04), whereas there were no significant interactions on EDE-Q subscale 1 “control of eating / drive for thinness”. In none of the four EDE-Q subscales a significant condition × diagnosis interaction was evident (subscale 1 “control of eating / drive for thinness” $F_{1,46.5}$=2.35, p=0.13; subscale 2 “urge to eat / fear of binge eating” $F_{1,41.9}$=1.76, p=0.19; subscale 3 “weight concerns” $F_{1,40.4}$ =0.72, p=0.40 and subscale 4 “feeling fat / body dissatisfaction” $F_{1,46.0}$=1.98, p=0.16).

The type of environment (controlled vs. uncontrolled) had a significant influence on the experience of bulimic symptoms also regarding EDE-Q subscale 1 "control of eating / drive for thinness" (environment × diagnosis interaction, $F_{1,218.7}$=4.02, p=0.04) and subscale 4 "feeling fat / body dissatisfaction" ($F_{1,210.8}$=4.19, p=0.04).

In subsequent analyses, the effects of past episodes of depression, anorexia nervosa and intake of psychotropic drugs on EDE-Q scores were analyzed within the rBN group. No significant effects were evident.

Baseline mean (SD) EDE-Q global scores were for rBN subjects: drug= 4.05 (5.66), placebo= 3.62 (3.12); and for controls: drug= 1.79 (2.14), placebo= 1.99 (2.40). A significant effect of diagnosis was evident in EDE-Q baseline scores ($F_{1,47.0}$=5.05, p=0.029), while there was no diagnosis × condition interaction (rBN $F_{1,47.0}$=0.495, p=0.485).

Regarding depressive symptoms assessed by the MADRS, in the controlled environment, the effects of AMPT on MADRS scores did not differ between diagnostic groups (condition × diagnosis interaction $F_{1,42.2}$=1.02, p=0.32). A significant effect of diagnosis ($F_{1,47.1}$ =6.63, p=0.01) and an effect of drug with a higher mean value in the AMPT condition compared to the placebo condition ($F_{1,42.1}$ =4.92, p=0.03) were evident. To investigate the depressive response to AMPT in rBN individuals with a history of MDD, we specifically compared rBN-MDD subjects with rBN-only subjects. In the controlled environment there was a difference in the MADRS response to AMPT between these two groups (condition × diagnosis interaction $F_{1,17.1}$=12.5, p=0.003). Compared to placebo medication rBN-MDD subjects reported a significant increase in depressive symptoms under AMPT ($F_{1,16.4}$=12.1, p=0.003) while this was not the case for rBN-only subjects ($F_{1,15.1}$=0.85, p=0.37). Baseline mean (SD) MADRS scores were for rBN subjects: drug= 2.83 (3.48), placebo= 2.61 (2.77); and for controls: drug= 0.52 (0.99), placebo= 1.16 (2.83). A significant

effect of diagnosis was evident in MADRS baseline scores ($F_{1,47.0}$=9.39, p=0.004), while there was no diagnosis × condition interaction (rBN $F_{1,47.0}$=0.996, p=0.323)

Hypomanic symptoms as assessed by the YMRS (across all time points), were significantly higher in rBN subjects relative to controls ($F_{1,61.0}$=7.07, p=0.01). A significant effect of drug was evident across groups ($F_{1,94.8}$ =8.82, p=0.004). However, there was no significant condition × diagnosis interaction ($F_{1, 94.8}$=1.96, p=0.16).

Regarding anxiety symptoms assessed by the BAI, in the controlled environment no effect of diagnosis ($F_{1,51.1}$=0.17, p=0.68), no effect of drug ($F_{1,89.1}$=0.15, p=0.70) and no significant condition × diagnosis interaction ($F_{1,89.1}$=0.39, p=0.53) was evident.

Concerning the ability to experience pleasure as assessed by the SHAPS, in the controlled environment, there was no effect of diagnosis ($F_{1,39.2}$=0.23, p=0.64), no effect of drug ($F_{1,111.2}$=0.62, p=0.43) and no significant condition × diagnosis interaction ($F_{1,111.2}$=1.70, p=0.19).

In the controlled environment, rBN subjects had higher sleepiness scores assessed by the SSS than controls ($F_{1,46.7}$=11.74, p=0.001). Across groups, AMPT induced more sleepiness than the active placebo with a total of 100mg diphenhydramine ($F_{1,47.3}$=9.49, p=0.003). However, no significant condition × diagnosis interaction was evident ($F_{1,47.3}$=0.48, p=0.49).

In the controlled environment the covariates MADRS ($F_{1,117.4}$=0.21, p=0.65), YMRS (across all time points; $F_{1,106.5}$=1.68, p=0.19), BAI ($F_{1,116.2}$=0.93, p=0.34), SHAPS ($F_{1,77.2}$=0.45, p=0.50) and SSS ($F_{1,97.9}$=0.79, p=0.37) had no significant effect on bulimic symptoms as assessed by the EDE-Q global score.

Serum prolactin levels were significantly higher in the AMPT condition versus the placebo condition (mean (SD), 42.0 (2.5) vs 29.5 (2.6) µg/L; $F_{1,36.5}$=20.93, p<0.001). There was no diagnosis effect ($F_{1,39.3}$=0.09, p=0.76) and no diagnosis × condition interaction ($F_{1,36.5}$=0.16, p=0.69) regarding serum prolactin concentration.

Discussion

To our knowledge, this is the first study that examined the behavioral effects of CD in BN. The results indicate that CD induced a transient reappearance of mild eating disorder symptoms in remitted subjects with a history of BN. Moreover, the induction of mild BN symptoms through exposure to the uncontrolled environment is consistent with persistent vulnerability to BN in fully remitted subjects (28). Contrary to our hypothesis, we did not find any significant condition × diagnosis interactions regarding depressive, manic, anxiety, anhedonia and sleepiness symptoms in rBN. As in our previous CD study in fully remitted subjects with MDD (7), rBN subjects with a MDD history showed a significant return of depressive symptoms following CD. This results suggest that depression comorbid with BN has no different neurochemistry than major depression alone.

Several types of indirect evidence suggest that dysfunction of the central noradrenergic system contributes to the risk of BN. A study with BN subjects abstinent from bingeing and vomiting (29) showed reduced basal plasma and cerebrospinal fluids, suggesting that noradrenergic disturbance might be a trait-like characteristic of BN. The effectiveness of noradrenergic antidepressants in BN (30) underlines the clinical relevance of these findings. Altered DA activity in BN has been identified even though the evidence is less consistent. Low DA metabolite concentrations in cerebrospinal fluid have been reported in BN subjects with frequent binge episodes (31, 32). In addition, highly palatable foods induce potent release of DA into the nucleus accumbens (33), similar to drugs of abuse, and DA is a key neurotransmitter in novelty seeking and the development of addiction (4), which suggests that abnormal DA activity may contribute to binge-eating episodes and other impulsive behaviours associated with BN. A study using positron emission tomography with [11C]raclopride detected decreased striatal DA neurotransmission in patients with BN relative to controls, a similar pattern to that described in addiction disorders (34). This finding may relate to reward

processing dysfunctions that has been found in remitted BN. Moreover, in rBN an fMRI study using a glucose taste paradigm found reduced anterior cingulate cortex activity, an area that is involved in error monitoring but also in the anticipation of reward, compared with controls (35). These results suggest that DA related reward processing dysfunctions are trait-like characteristics associated with BN.

Several strengths of the current study deserve mention. While in previous studies using AMPT doses greater than 4g, subjects experienced adverse reactions such as dystonic reactions (36), restlessness (37), crystals in urine and decreased blood pressure (38), none of our participants reported any significant adverse reactions, probably due to the use of a low, body weight-adjusted AMPT dose. The sample size was relatively large for a complex pharmacological challenge study. The use of an active placebo (diphenhydramine) to mimic the side effects of the experimental drug (AMPT) contributed to an effective blinding of the study drug and reduced the potentially confounding effect of sleepiness, one of the main adverse effects of AMPT, on psychiatric ratings. As expected, CD-induced sleepiness did not correlate with CD-induced bulimic symptoms. The fact that CD induced the same amount of prolactin in rBN subjects and healthy controls suggests that there was no difference of the CD effect on catecholamine synthesis between groups (39).

Some limitations of this study should be considered. The psychiatric symptoms induced by CD were minor, which calls the clinical relevance of the findings into question. However, using the same low, body weight-adjusted AMPT dose, a previous study in fully remitted subjects with major depressive disorder (MDD) also induced only mild depressive symptoms, which helped to elucidate a neurocircuitry that plausibly relates to the catecholamine-related pathogenesis of depression (7). A previous tryptophan depletion (TD) study also induced only minor bulimic symptoms in rBN (17), suggesting that this is a general limitation of modern monoamine depletion studies using safe and ethically justifiable dosages. Our cross-sectional design could not establish whether the bulimic response to CD in rBN

reflected an endophenotypic vulnerability to eating disorders or a consequence of illness. The lack of more objective outcome measurements represents a shortcoming of this study. The inclusion of a food challenge would have provided more reliable data. The inclusion of lab values such as potassium would have contributed to a more objective definition of recovery. We did not reliably assess the phase of the menstrual cycle and subjects were tested in both the follicular and luteal phases, which may represent a potentially confounding factor. However, a previous study did not reveal any effects of the menstrual cycle on CD-induced symptoms (7). As a result of the inclusion criterion that rBN subjects had to be in remission and off medication, a selection bias may have been introduced, resulting in a sample with relatively mild forms of BN. Although the results of subsequent analyses considering the impact of past episodes of depression, anorexia nervosa and intake of psychotropic drugs on EDE-Q scores did not indicate a significant effect, the influence of these potentially confounding variables cannot be ruled out because of the insufficient power of the stratified analyses. In the controlled environment the condition x diagnosis interaction was absent. However, in the uncontrolled environment, catecholamines were not expected to be depleted anymore. As a result, this study does not provide insights into the interaction of drug condition, diagnosis and uncontrolled environment. Not correcting for experiment-wise error represents another limitation of the study; as a result, the findings should be interpreted as exploratory. Finally, the specificity of our results was limited by CD's effect of reducing synthesis of NE as well as DA.

The provocation of mild BN symptoms by CD suggests that BN is associated with persistent vulnerability for developing eating disorder symptoms in response to reduced catecholamine neurotransmission. The absence of significant condition × diagnosis interactions regarding mood and anxiety symptoms suggests that disease-specific risk factors rather than reduced catecholamine neurotransmission per se determine the type of symptoms induced by CD.

Given the extensive interconnection among the monoamine systems, the specificity of the contribution of serotonin, norepinephrine and dopamine dysfunctions to psychiatric conditions has been a matter of debate. In fully remitted subjects with major depressive disorder, CD induced similar symptoms as tryptophan depletion (7, 40), although some differences emerged: CD induced less depressed mood and sadness, but more lassitude and anxiety than TD (Hasler et al., unpublished data). In the previous TD study in rBN (17), TD induced significantly more depressive symptoms as measured by the Hamilton Depression Rating Scale (HAM-D) in rBN than in controls. Even though caution is required in combining findings from TD studies with results of this study, behavioral responses to CD and TD seem to be similar in rBN subjects and controls. Differences between studies may suggest that catecholamine activity might be more specifically related to eating disorder psychopathology than serotonin activity in rBN. Stratified analyses suggest that differences between the two studies were not related to the higher rate of rBN subjects with a history of MDD in the TD than in this CD study.

CD did not induce depressive and anxiety symptoms in rBN subjects. This is in contrast to previous studies on the central serotonergic dysfunction in BN, demonstrating that TD induced non-specific mood symptoms in rBN (16, 17). Together, these findings suggest that the relationship between central catecholaminergic neurotransmission and bulimic symptoms is relatively specific in rBN.

In summary, the present findings indicate that decreased catecholaminergic neurotransmission after CD may trigger the transient reappearance of eating disorder symptoms in individuals vulnerable to BN. This result supports the assumption of a catecholaminergic dysfunction in the pathophysiology of BN. Further investigations are encouraged to elucidate the neural and genetic underpinnings of this potential trait-like dysfunction.

Acknowledgments

This research was supported by the Swiss National Science Foundation Nr. 32003B-117763.

Financial Disclosures

No conflicts of interest.

Simona Grob and Gregor Hasler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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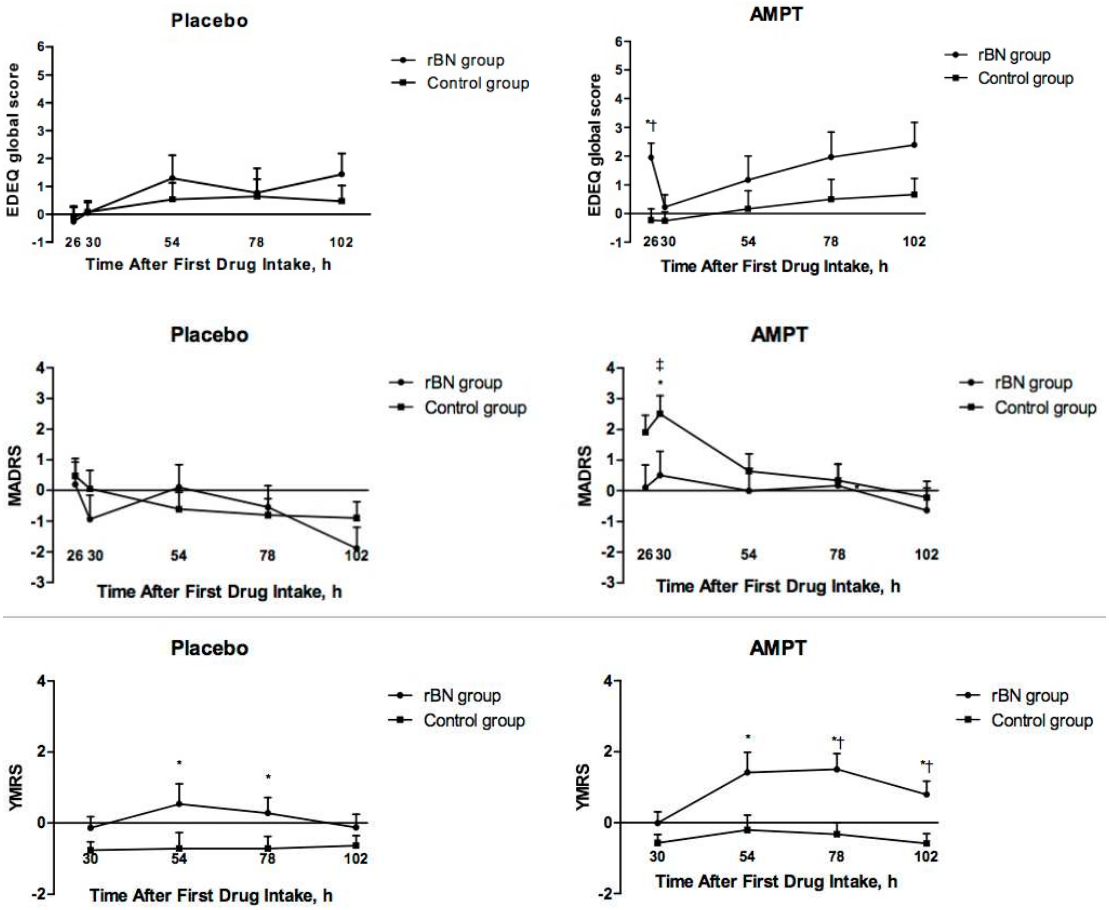
Table 1. Demographic and Clinical Characteristics of Unmedicated Subjects with rBN and Healthy Controls*

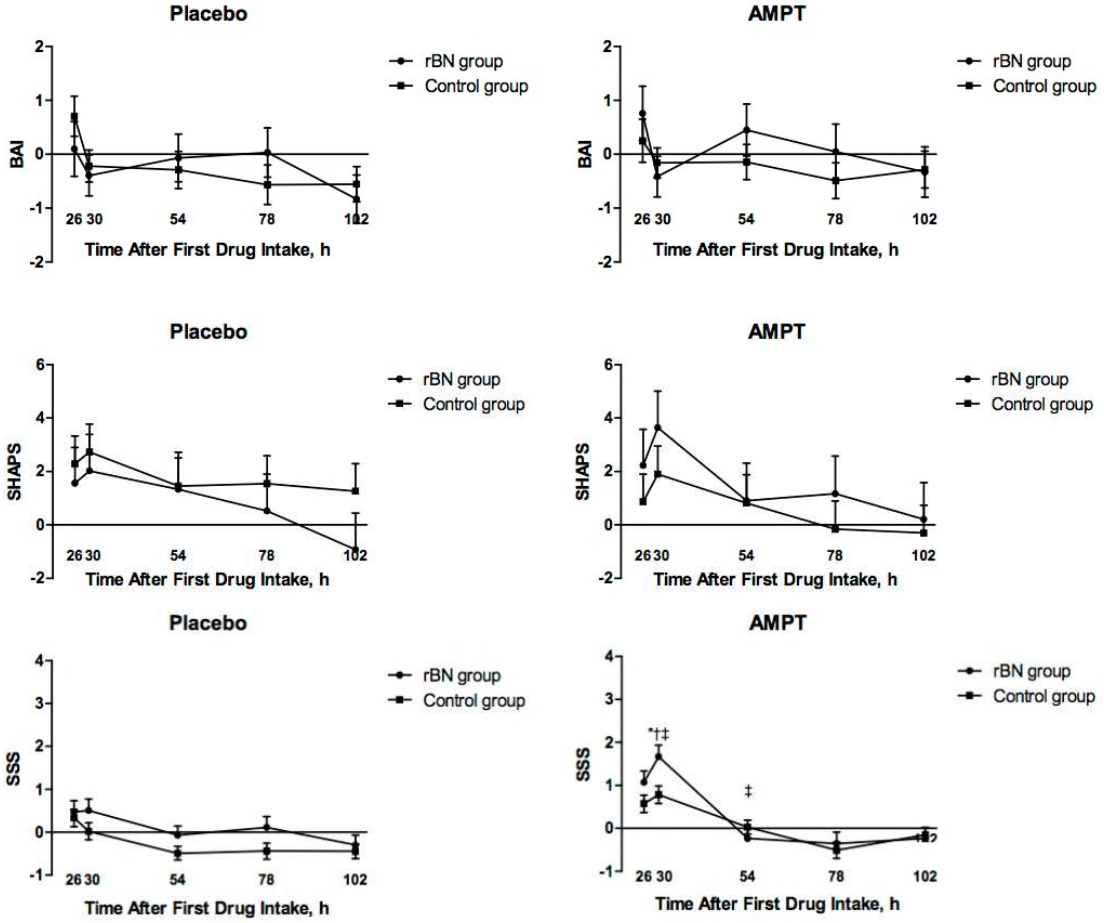
Characteristic	rBN Subjects (n=18)	Controls (n=31)
Sex	F	F
Age, mean (SD), y	25.6 (4.7)	25.8 (3.8)
Age at onset, mean (SD), y	14.4 (4.2)	NA
Body mass index, mean (SD), kg/m²	21.2 (1.7)	22.4 (2.2)
Range, kg/m²	*18.3-24.7*	*18.6-26.6*
Time in remission from Bulimia Nervosa, mean (SD), mo	29.2 (23.6)	NA
Range, mo	*6 - 84*	*NA*
Major Depression preceding or during BN (No. of Subjects)	4	NA
Previous Anorexia Nervosa (No. of Subjects)	6	NA
Time in remission from Anorexia Nervosa, mean (SD), mo	98	NA
Range, mo	*36-132*	*NA*
Previous use of psychoactive medication, SSRI, TCA, (No. of Subjects)	6	0
Time medication free, mean (SD), mo	10 (3.5)	NA
Range, mo	*6 - 12*	*NA*

Abbreviations: NA, not applicable; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; rBN, bulimia nervosa in remission.

* Subjects with rBN and control subjects did not differ significantly in age and body mass index

Figure 1. Behavioral Responses to Catecholamine Depletion and Placebo in Unmedicated Subjects with Bulimia Nervosa in Remission (rBN group) and Healthy Control Subjects. *=Significant diagnosis effect (rBN vs Controls, p<.05); †=significant condition effect for rBN; ‡=significant condition effect for Controls; rBN subjects n= 18, control subjects n=31. Behavioral ratings are shown as changes scores that were calculated by subtracting baselines scores from raw scores of each time point in order to increase visibility of depletion effects.




Placebo
AMPT
rBN group
Control group
BAI
SHAPS
SSS
Time After First Drug Intake, h
26 30
54
78
102
*†‡
‡